REMARKS

Applicants respectfully request reconsideration and withdrawal of the rejections set forth in the Office Action. Claims 40-43, 48-52 and new claims 58-59 are now pending in this application.

The specification has been amended as requested.

Rejection of claims under 35 U.S.C. §112

Claims 40-43 and 48-52 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claims 40 and 48 have been amended to recite method steps disclosed in the specification (specification page 22, lines 16-21). Claims 58-59 were added using the term "identified" in the claims and the method of identification is described in the specification (specification page 14, lines 5-33). The term derived was maintained in claims 40 and 48 because this term is recognized in the antibody field. A brief search of the USPTO website located 1,270 patents using the word derived in claims directed to an antibody. In light of the foregoing amendments to the claims, this rejection for indefiniteness should be withdrawn.

Rejection of claims under 35 U.S.C. §102(b)

Claims 40-42 and 48-50 were rejected under 35 U.S.C. §102(b) as being anticipated by Adair et al.

The Adair et al. reference discloses the identities of important residues in the framework of variable regions for obtaining CDR-grafted products with satisfactory binding affinity. While it does disclose the various residues that were determined to be important for an antibody with general binding affinity, it does not indicate which ones are important for antibodies with specificity for medulloblastoma cells. Because selective identification of these cells and targeting them apart from normal brain tissue or peripheral blood cells is extremely important when it comes to treating brain tumors, an antibody that will not cross-react with these surrounding cells is necessary. In order to produce a reshaped antibody to a

specific antigen that has sufficient binding activity, the appropriate amino acid sequence including the exact mouse residues needed must be identified (specification page 5, lines 4-13). Presently there are no methods for producing a reshaped human antibody to a specific antigen that has sufficient binding activity (specification page 5, lines 7-10). The present invention teaches the exact residues that are necessary for sufficient activity in a humanized monoclonal antibody with specificity for medulloblastoma cells.

Further, the Adair et al. reference was published July of 1991 and research presented in 1993 (Moriuchi, S. et al.) searching for a successful monoclonal antibody for medulloblastoma cells concluded that research remain to be conducted regarding the sequences of the three hypervariable region CDRs of the ONS-M21 which are the antigen recognition sites for the L chain and the H chain. The fact that in 1993 the antigen recognition sites to make a humanized antibody specific for medulloblastoma cells were still unknown demonstrates that the Adair reference did not provide information necessary for a person of ordinary skill to create an antibody as presently claimed. A non-enabling reference cannot anticipate.

In light of the lack of a specific disclosure in the Adair reference detailing which specific residues need to be present to have sufficient activity towards a medulloblastoma cell and, in light of the further research being suggested after the publication of this reference, the rejection for anticipation by Adair should be withdrawn.

Rejection of claims under 35 U.S.C. §102(e)

Claims 40, 43, 48 and 51 were rejected under 35 U.S.C. § 102(e) as being anticipated by Seemann et al. This reference teaches the use of proline as the mouse donor residue in position 46 on the L chain but only specifies that, with the exception of colon mucosa, the mouse proline residue may be exchanged with alternate mouse donor residues. This reference, unlike the present invention, does not teach that proline in position 46 on the L chain necessarily would increase the ability of the reshaped antibody to bind to the medulloblastoma cells.

Rejection of claims under 35 U.S.C. §103

Claims 40-43 and 48-52 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Adair et al. in view of Seemann et al. or Huston et al. It would not have been obvious to combine these prior art references and to create a humanized antibody specific for medulloblastoma cells having sufficient binding activity.

"Obviousness can only be established by combining...the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP § 2143.01.

As presented above, Adair discloses a multitude of optional residue designations to create a humanized antibody molecule with satisfactory binding affinity. As argued previously, Seemann et al. teaches the use of proline at residue position 46 on the L chain, but does not teach that a proline mouse donor residue at this position should be incorporated to provide an antibody created specifically targeting medulloblastoma cells. There was no motivation to combine these two references to create an antibody with specificity for medulloblastoma cells. In fact, Seemann et al. specifies one instance with respect to colon mucosa where it was necessary to not alter the proline mouse residue which suggests that proline does not greatly affect the specificity of other antigen binding sites. Further, it was not obvious that the specific linker set forth in Huston et al. and claimed in claim 48 combined with the two previous prior art references would create an antibody specific to medulloblastoma cells with satisfactory binding affinity.

Claims 40-43 and 48-52 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Moriuchi et al., and further in view of Adair et al. and Huston et al. Moriuchi teaches the general proposition that ONS-M21 would be helpful to produce a humanized antibody but does not identify the sequences of the three hypervariable region CDRs which are the antigen recognition sites. As mentioned above, Adair teaches a multitude of possible mouse residues that are important for obtaining satisfactory binding affinity in a humanized antibody but does not identify which mouse residues provide sufficient binding activity for an antibody with specificity for medulloblastoma cells. It would not be obvious to combine the Adair

reference and the Moriuchi reference to obtain which mouse residues would provide satisfactory binding affinity for an antibody specific for medulloblastoma cells. Further, it would not have been obvious to combine the Huston et al. reference which teaches producing single chain Fvs and a linker. There was no motivation to combine the references in the prior art and, therefore, the rejection for being unpatentable under 35 U.S.C. § 103(a) is incorrect.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

MARKED UP VERSION SHOWING CHANGES MADE

Below is the marked up version showing the changes to the specification:

Page 1, paragraph 1 lines 3-6.

This application is a Divisional of application Serial No. 08/646,265, filed September 9, 1996, **now U.S. Patent No. 6,214,973**, which is a national stage of PCT/JP94/01763, filed October 19, 1994.

Below is the marked up version showing changes to the claim(s):

40. (**Amended**) A method for making a reshaped human antibody comprising:

(a) providing complementary determining regions derived from a mouse antibody and framework regions derived from a human antibody, [~~and~~]

(b) substituting an amino acid residue of position 46 of an L chain numbered according to Kabat [~~et al.~~] as a mouse antigen binding site, **and**

(c) substituting 0-5 amino acid residue(s) on an H chain numbered according to Kabat. with a mouse antigen binding site.

48. (**Amended**) A method for making a single-chain Fv region comprising:

(a) producing a reshaped antibody [~~H chain V region and L chain V region, which are linked~~] **by substituting an amino acid residue on position 46 of an L chain V region numbered according to Kabat, as a mouse antigen binding site and by substitution 0-5 amino acids on the H chain V region, numbered according to Kabat, with a mouse antigen binding site,**

(b) linking the L chain V region and the H chain V region with a linker peptide, and [~~have complimentary~~]

(c) combining identified complementary determining regions from a mouse antibody and framework regions derived from a human antibody, wherein an amino acid residue 46 of L chain V region numbered according to Kabat [~~et al.~~]is a mouse residue and the single chain Fv region creates a functional antigen binding site.